Security Classification

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified.

1. ORIGINATING ACTIVITY (Corporate author): 6570 Aerospace Medical Research Lab., Aerospace Medical Div., AFSC, Wright-Patterson AFB, OH 45433.

2a. REPORT SECURITY CLASSIFICATION: Unclassified

2b. GROUP:

3. REPORT TITLE: Toxicological Evaluation of Carbon Monoxide in Humans and Other Mammalian Species.

4. DESCRIPTIVE NOTES (Type of report and inclusive dates):

5. AUTHOR(S) (First name, middle initial, last name):
Maj James Theodore, USAF, C.C.
Capt Robert D. O'Donnell, USAF
Kenneth C. Back, PhD.

6. REPORT DATE: May 1971

7a. TOTAL NO. OF PAGES: 14

7b. NO. OF REFS: 40

8a. CONTRACT OR GRANT NO.:

8b. PROJECT NO: 6302/02

9a. ORIGINATOR'S REPORT NUMBER(S): AMRL-TR-71-6

9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report):

10. DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited.

11. SUPPLEMENTARY NOTES: Reprinted from JOURNAL OF OCCUPATIONAL MEDICINE, Vol 13, No. 5, May 71.

12. SPONSORING MILITARY ACTIVITY:

13. ABSTRACT

AD 725203

DD FORM 1 NOV 65 1473

Security Classification

Toxicological Evaluation of Carbon Monoxide in Humans and Other Mammalian Species

MAJ. JAMES THEODORE, USAF, M.C.
CAPT. ROBERT D. O'DONNELL, USAF
KENNETH C. BACK, Ph.D

Major Theodore is with the Division of Respiratory Medicine, Department of Medicine, Stanford School of Medicine, Stanford, California.

Captain O'Donnell is with the Space Biology Laboratory, Brain Research Institute, UCLA Health Sciences Center, Los Angeles, California.

The studies reported here were part of a major cooperative effort, representing a composite of works from members of the Toxicology and Pathology Branches of the Toxic Hazards Division and its facility contractor, the SysteMed Corporation. The human studies were carried on jointly by the Toxic Hazards and Human Engineering Divisions of the Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio. This paper has been identified by Aerospace Medical Research Laboratory as AMRL-TR-71-6. Further reproduction is authorized to satisfy needs of the U.S. Government. The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965. The voluntary informed consent of the subjects used in this research was obtained as required by Air Force Regulation 169-8.

Carbon monoxide has become an important by-product of the advances of modern technology. Dinman[1] deduced if adaption or evolutionary change is a first-order reaction, and the rate of technological change is logrithmic, that man may create an environment incompatible with his evolved ability to exist. This prospect has evoked concern in the general area of atmospheric pollution and in the specific area of community air quality standards for carbon monoxide. Thus studies concerning the effects of chronic exposure to relatively low levels of carbon monoxide upon the health of the general population are of great importance. In addition, this potential risk applies to military populations in a number of operational systems. This risk is especially important in the aerospace environment where human performance is carried to its extreme limits in high performance aircraft and in space systems. Therefore, the need to establish realistic criteria for carbon monoxide effects on man is also essential to the complex military systems of today.

This presentation is not intended to be an extensive review dealing with all aspects of carbon monoxide toxicity. The interested reader is referred to several reviews[2-5] and to the recent New York Academy of Sciences symposium "The Biological Effects of Carbon Monoxide,"[6] which explored the subject in great depth. This discussion will deal primarily with those areas of interest where controversy has existed, and will concentrate on reviewing recent work done at the Toxic Hazards Division of the 6570 Aerospace Medical Research Laboratory at Wright-Patterson Air Force Base, Ohio.

Although the toxicity of carbon monoxide was well established, the Air Force developed a keen interest as a result of the following considerations.

1. Once the reality of man in space was established, it soon became apparent that carbon monoxide might become a major problem on long-term space flights, i.e., missions of greater than 90 days duration. Studies on space cabin materials revealed that a major gas-off product was CO. Of the first 206 materials tested, 127 or 62 per cent evolved CO.[7-9] Another potential source of CO contamination stemmed from considerations of O_2 regeneration systems, which would be needed for long missions. Such systems could utilize the Sabatier reaction or others which utilize CO in the reaction cycle to generate O_2. Finally, man himself would contribute to the CO. Coburn studied endogenous CO production and the CO pool in man.[10] He measured the rate of endogenous CO production at 0.42 ml/hr in a normal resting male, with production primarily from hemoglobin catabolism.

2. The detrimental effects of CO have been primarily derived from acute exposures to relatively high concentrations. Under such circumstances the central nervous system (CNS) is the most vulnerable, followed by cardiovascular collapse late in the intoxication

cycle.[10] Although these effects are part of an acute CO exposure, this same relationship does not necessarily apply to chronic (intermittent) or continuous exposures to low concentrations of CO. The major question at present is, "Does chronic continuous exposure to CO adversely affect the CNS or the cardiovascular system at low levels which are considered safe during transient exposures?"

3. Since the CNS is the most sensitive to hypoxia, could CO disrupt the more complex cognitive mental or the highly integrated functions of the brain? Several studies report decrements in human performance with COHb levels as low as 3 to 5%.[11-13] These will be discussed later in more detail; however, others have not seen impairment at these levels.[14-16] The importance of determining whether real effects from CO exist at such low levels of COHb becomes apparent when the COHb levels of cigarette smokers are taken into consideration. Goldsmith and Landaw found smokers to have blood COHb levels between 3.8 and 6.8%.[17] If these COHb levels are compared to the 3 to 5% levels associated with performance decrements as reported by several investigators, then one must consider the possibility that large segments of the population may be performing certain functions at depressed levels.

In an attempt to answer some of the questions posed, the Air Force has been studying these facets of CO toxicity since 1967. This report essentially reviews that entire experience. The studies can be divided into three major areas: (1) the effects of continuous long-term CO exposure on various animal species; (2) the effects of continuous long-term CO exposure on the performance of rhesus monkeys; and (3) the effects of short-term low level CO exposure on human performance. Each of these areas will be described separately. The pertinent literature is discussed concurrently as it applies in each section.

The Effects of Continuous Long-Term Carbon Monoxide Exposure on Various Animal Species

A variety of animals were selected for this study. Rhesus monkeys, baboons, dogs (Beagles), rats and mice were exposed to CO continuously for 168 days in the Thomas Domes[18] at 5 psi in a mixed gas atmosphere (68% O_2, 32% N_2).* The exposed animals received CO at concentrations of 460 mg/cu m for the first 71 days, followed by 575 mg/cu m for the remaining 97 days. These animals were compared to controls which were maintained under identical conditions, except for the presence of CO. These relatively high levels of CO were selected with the purpose of trying to induce abnormalities in order to provide guidelines for more specific work.

An extensive number of parameters were measured as outlined in Table I. Those listed as preliminary comprise studies that are continuing. At present the small number of observations does not permit specific statements, but appropriate trends can be mentioned. In addition to noting abnormalities, this broad approach permits detection of major adaptive processes which may occur.

TABLE I

PARAMETERS MEASURED DURING CONTINUOUS 168-DAY CARBON MONOXIDE EXPOSURE

Hematology (dogs, monkeys)
COHb sat.
CBC
Indices
Retic.
RBC frag.
Blood viscos.
Blood volume (RBC vol. + plasma vol.)
Marrow
Clinical chemistry (dogs, monkeys)
Ca, Na, K, Cl
Tot. chol.
Inorg. p.
Tot. bilirubin
Tot. protein
Alb.
Creatinine
Uric acid
BUN
Glucose
LDH
Alk. p.
SGOT
Gross pathology (all species)
Histopathology (all species)
Preliminary physiological and brain metabolic measures (limited number of measurements)

Blood COHb Levels: Under these steady state conditions, moderately high blood carboxyhemoglobin (COHb) levels were achieved. At each level of CO exposure, the corresponding COHb reached equilibrium within the respective two-week sampling period.† These measurements were made only on dogs and monkeys. At the 460 mg/cu m CO exposure level, the COHb level in monkeys was 32% saturation, and in dogs 33%; at 575 mg/cu m, the monkeys had 38% COHb, and the dogs 39%. These moderately high levels were maintained over the entire 168 days and provided an adequate test for CO effects. Although the COHb levels

*Although these studies were done at reduced barometric pressures, the 68% O_2 at 5psi results in a partial pressure of O_2 that is slightly greater than that found at sea level.

†Due to the number of measurements requiring blood, the samples were drawn every two weeks during the entire study. In the interim periods, blood COHb levels should be relatively stable since the blood COHb reaches equilibrium with the inspired CO within 24 hours.[19]

TABLE II

SURVIVAL DURING CARBON MONOXIDE EXPOSURE CONTINUOUSLY FOR 168 DAYS

CO conc. 480 mg/cu m for 71 days 575 mg/cu m for 97 days

Atmosphere 5 psi, 68% O_2, 32% N_2

Species	CO-Exposed	Control
Monkeys	4/0*	5/1
Baboons	2/0	1/0
Dogs	8/0	8/0
Rats	68/5	68/2
Mice	40/0	40/1

Days of deaths: CO group – rats, 59, 107, 159, 166, 166
Control - monkey, 108, rats, 54, 116, mouse, 64

* Number of animals/number of deaths

were not determined in the rodents, their COHb levels by past experience are probably comparable to those of the species measured.

Survival: Despite the COHb levels reached, the animals showed a remarkable ability to survive. Table II summarizes the mortality data for the entire exposure. Of significance was the relative paucity of deaths in the CO group. Comparing the two groups reveals essentially no difference in over-all mortality. In the CO group only five rats died, with no deaths occurring in the other species. Among the controls, three rodents died (two rats, one mouse) along with the only primate death in both groups. Four of the five rat deaths in the CO group occurred in the final third of the exposure, whereas control deaths were more evenly distributed. Although this might tend to implicate CO, the small numbers involved on the whole tend to reduce the significance of this. In toxicological mortality studies, the number of deaths that occurred among rodents in both groups can be expected by chance alone, due to the high incidence of intrinsic disease in rodent populations.

The two rats that died at 166 days in the CO group showed dilated left ventricles and generalized congestion. The three others in the CO group were of little value because of postmortem autolysis. In summary, carbon monoxide under these conditions did not significantly influence the mortality rate.

Growth Rates: Body weights were measured on all animal species every two weeks during the course of the exposure. Weight gain can be a sensitive index of growth rate if the measurements are made during the logrithmic phase of growth. In this case, the rat serves as an ideal model since it can be readily studied during that phase. Furthermore, during exposure studies which last 24 weeks, the relative short life cycles of rats permit a greater fraction of their life span to be stressed than would be the case in larger animals.

Fig. 1 shows the rate of weight gain for both the control and CO-exposed rats. Although there is slight separation of the two curves, especially when the CO concentration is at the 575 mg/cu m level, both groups were equivalent at the conclusion of the exposure. In general, considering the entire exposure, carbon monoxide did not influence weight gain. Similarly, the other animal species showed no adverse effects from CO with respect to body weight.

Clinical Chemistry: Serial measurements of these parameters (see Table I) permit, at the least, a general estimate of the over-all state of dynamic equilibrium maintained by numerous internal processes. Although these measurements are not the most sensitive index of subtle change, major distortions of physiologic or biochemical steady states can certainly be detected. Serial measurements taken before, during and after the exposure failed to show any significant differences between the two exposure groups, nor any within each group over the entire period of observation.

Brain Metabolic Studies: Preliminary studies in our laboratory by George, Murphy and Back have been undertaken to note if CO-exposed monkeys develop

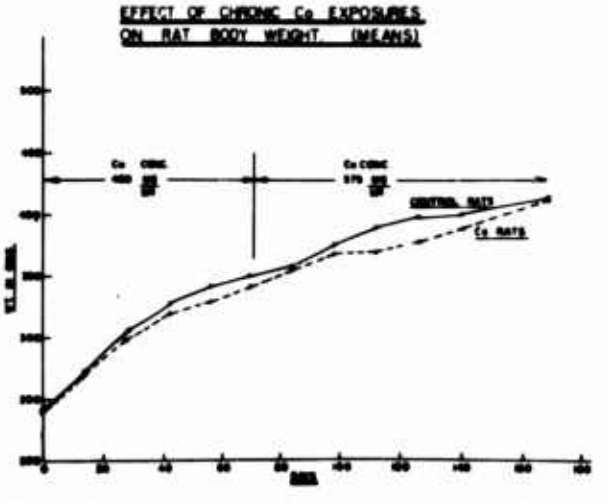

Fig. 1. The mean weights of the exposed and control rats plotted over the course of the 168-day CO exposure.

distortions in brain enzyme systems involved in oxidative energy production.[18] Brain tissue levels of creatine phosphate, ATP, ADP, AMP, inorganic phosphate and pyridine nucleotides were measured, along with respiratory control studies on brain mitochondrial preparations following two-week exposure at 220 and 440 mg/cu m. No significant changes were noted; however, at present this represents too few studies to be definitive.

Pathology: In classic toxicology, pathologic studies have always played one of the major roles in the total evaluation. At this point, we would like to make a plea that probably needs more emphasis. Too frequently pathologic studies are carried on in a wide variety of animal species without intimate knowledge of the intrinsic disease unique to each species. Lesions in animals do not necessarily correspond to those in humans. MacKenzie[19] recently stressed the number of artifacts that can be induced into animal pathology by such things as improper tissue handling, feeding animals on the day of sacrifice, or by the method of sacrifice. It is important that those engaged in this kind of work be intimately familiar with the particular species under study, or at least have available to them consulting veterinary pathologists or those human pathologists having great experience with animals.

The primary reason for the selection of the relatively high CO levels for this study was to try to induce chronic changes in the central nervous system and heart. These two systems have been reported to be the most severely involved in CO intoxication. Pathological changes that have been reported most frequently in the brain are of the type noted with severe hypoxia from any cause. In acute fatal CO intoxication in humans, the most frequent changes are generalized congestion and edema of the tissues. The brain shows edema, focal and petechial hemorrhages, and areas of necrosis. Those areas most frequently involved are the basal ganglia, especially the globus pallidus, the subcortical white matter, Ammon's horn of the hippocampus, and, less frequently, parts of the cerebellum and the brainstem.[20] The heart showed petechial hemorrhages most frequently, especially in the epicardium.[20]

There have been reports that dogs chronically exposed to CO also develop CNS and cardiac changes. Lewey and Drabkin[21] reported disturbances in gait and in position and postural reflexes in dogs exposed to 115 mg/cu m of CO for 5 3/4 hours per day, six days a week, for 11 weeks. These animals showed CNS changes which included necrosis and demyelination in the white matter of the cerebral hemispheres, the globus pallidus and brainstem. The COHb found in these animals was reported to be 20%. This appears to be high for their exposure concentrations and schedule of administration in the light of our experience. Lindenberg et al.[13] exposed dogs either continuously or intermittently for six weeks to 58 mg/cu m of CO. They reported glial mobilization and dilation of the lateral cerebral ventricles. They suggested that these changes were part of a chronic process secondary to cardiac decompensation.

Ehrich, Bellet and Lewey[24] reported EKG changes and myocardial muscle fiber degeneration in dogs exposed to 115 mg/cu m of CO for 11 weeks under the same conditions noted above for Lewey and Drabkin. The COHb in these dogs was 21%. Lindenberg et al.[13] reported EKG changes at 58 mg/cu m and at 115 mg/cu m of CO. Their most frequent finding at autopsy was right ventricular dilation and, in some hearts, muscle fiber degeneration. Their dogs exposed to 58 mg/cu m of CO had COHb of 2.6 to 5.5%. Musselman,[15] on the other hand, exposed rats, rabbits and dogs continuously for three months to 58 mg/cu m of CO and found no EKG changes and no pathologic differences between the exposed and control animals.

In our study, all of the CO-exposed and control animals were sacrificed for pathologic study. In general, the results have been relatively unimpressive. On gross examination, all the large animals showed no changes in the CNS or in the heart. There was some degree of generalized vascular congestion; however, since the hematocrits in these animals were all in the 60's, this is easily explainable. On gross examination, the only positive findings were found in the rats.

Table III summarizes the organ weights of rats, and, in essence, all of our positive findings. The mean heart and spleen weights of the CO group were significantly greater than the controls. Surprisingly, the liver and kidney mean weights in the CO group were less. When comparing organ to body weight ratios, the only significant weight changes were the increases in the hearts and spleens of the CO group. These findings can be partially explained by the marked erythrocytosis seen. Obviously, the vascular engorgement due to increases in blood volume can explain the higher spleen weights. In part, this can account for the cardiac hypertrophy as well, since cardiac work increases with larger blood volumes and with concomitant increases in blood viscosity encountered with hematocrits over 60. In addition to the increased heart weights, these rats also showed some degree of ventricular dilation. With this apparent cardiac involvement in rats, it was surprising to find that on gross examination the brains were normal.

Table IV lists those areas of the brain and heart which were evaluated. As previously mentioned, these areas of the brain are the most sensitive to CO or hypoxia as pointed out by Lapresle and Fordeau.[20] The numerous heart sections listed reveal the depth and extent of the analysis being undertaken to critically review the heart.

On gross pathologic review, all the brains, and indeed all tissues, of the large animals were normal. The histology of those areas listed above has been reviewed and there were no significant microscopic differences between the two groups. The hearts of these animals also revealed no histologic differences between the two groups. Of special interest were the aortas of these animals. Astrup has reported that CO induced

TABLE III

168-DAY CHRONIC CO EXPOSURE—MEAN RAT ORGAN DATA

Organ Weights (grams)

	Control (N = 28)*	CO-Exposed (N = 25)	Significant to .01 Level
Heart	1.2 ± .17	1.5 ± .25	Yes
Lung	1.5 ± .19	1.5 ± .19	No
Liver	10.5 ± 1.38	9.3 ± .98	Yes
Spleen	0.9 ± .23	1.1 ± .14	Yes
Kidneys	1.9 ± .21	1.8 ± .21	Yes

Organ to Body Weight Ratio

$$R = \frac{\text{Organ wt.}}{\text{Body wt.}} \times 100$$

	Control (N = 28)	CO-Exposed (N = 25)	Significant to .01 Level
Heart	.293 ± .035	.392 ± .061	Yes
Lung	.381 ± .042	.411 ± .051	No
Liver	2.575 ± .213	2.478 ± .181	No
Spleen	.232 ± .034	.295 ± .034	Yes
Kidney	.211 ± .034	.467 ± .046	No

* N = number of animals

TABLE IV

CHRONIC CARBON MONOXIDE EXPOSURE—HISTOPATHOLOGIC ANALYSIS

Sections of brain and heart surveyed

Brain sections

1. Basal ganglia—anterior
2. Basal ganglia—posterior, to include hippocampus, cerebral cortex, and subcortical white matter
3. Cerebral peduncles, midbrain, substantia nigra
4. Medulla and cerebellum at level of pons
5. Posterior medulla or upper cord

Heart sections

1. Right and left atria
2. Right and left ventricles
3. High intraventricular septum including portion of right atria
4. Papillary muscles
5. Ascending aorta

significant atheromatous changes in rabbit aortas.[36] However, in our animals, no atheromatous changes were detected in any of the aortas studied by gross or microscopic examination. The pathology data is to be published in its entirety in the near future.

At this point, we have not been able to reproduce the extensive changes seen by others, although we exposed our animals to higher concentrations of carbon monoxide and for a longer continuous period of time.

Hematology: The most impressive findings of the entire study were noted in the hematologic response to CO. Figs. 2 and 3 show the marked erythrocytic response to CO. The hemoglobin concentrations can be representative in this case, since the red cell counts and hematocrits show similar changes. The figures show the serial hemoglobin (Hb) concentration and reticulocyte counts in dogs and monkeys measured every two weeks in the CO group and the controls. The sharpest rise of mean Hb concentration occurred in the first four weeks for both species during the 460 mg/cu m CO exposure, with dog Hb increasing from a mean of 14.6 to 19.7 gm % and monkey Hb from 12.6 to 17.0 gm %. The change in Hb plateaus corresponded to the increase in the CO concentrations from 460 mg/cu m to 575 mg/cu m after 71 days. Following the increase of CO to 575 mg/cu m, both species reached their peak Hb levels at 20.2 gm % for monkeys, and 22.8 gm % for dogs. After 16 weeks of exposure, both species showed a decrease in Hb concentration. We have no good explanation for this phenomenon. It could represent a form of marrow failure, some hemolytic process, or simply the effects of multiple phlebotomies to acquire blood samples. Osmotic fragility curves done on the red cells of several

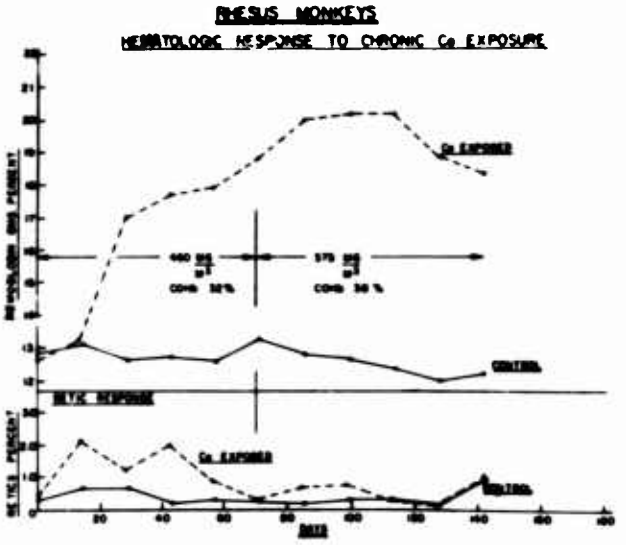

Fig. 2. Hemoglobin and reticulocyte response in control and exposed rhesus monkeys during continuous CO exposure.

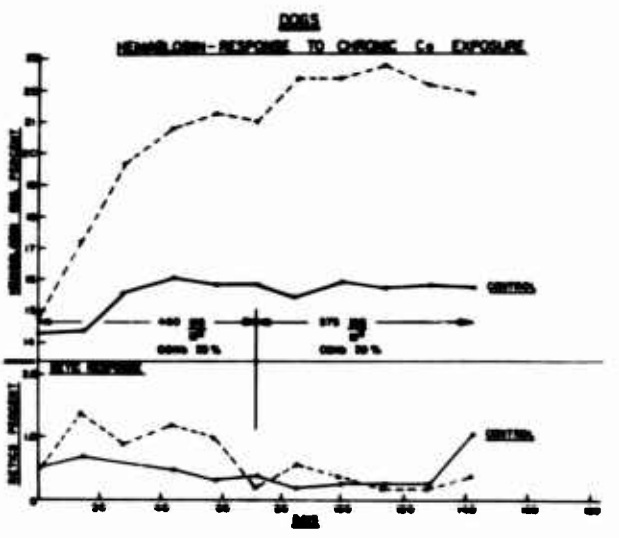

Fig. 3. Hemoglobin and reticulocyte response in control and exposed dogs during continuous CO exposure

TABLE V

EFFECTS OF CHRONIC CARBON MONOXIDE ON BLOOD VOLUMES

Animal No.	Body Wt.	RBC Vol. ml/kg	RBC Vol. (ml)	Pl. Vol. ml/kg	Pl. Vol. (ml)	Bl. Vol. ml/kg	Bl. Vol. (ml)	Calc. Hct.	Venous Hct.
Control–Dogs									
J-28	13.5 kg	37	(498)	53	(711)	90	(1,209)	47	46
J-26	13.5 kg	45	(604)	62	(833)	106	(1,437)	42	49
J-44	12.2 kg	36	(442)	58	(703)	94	(1,145)	39	44
J-42	13.3 kg	49	(653)	60	(798)	109	(1,451)	45	52
J-64	14.4 kg	45	(647)	55	(792)	100	(1,439)	45	50
Mean		42 ± 6 ml/kg		58 ± 4 ml/kg		100 ± 8 ml/kg		42 ± 3	48 ± 3
Carbon Monoxide Exposed–Dogs									
J-32	9.7 kg	72	(699)	58	(561)	130	(1,260)	56	65
J-48	12.6 kg	71	(894)	48	(609)	119	(1,503)	60	69
J-40	11.4 kg	86	(979)	53	(610)	139	(1,589)	62	70
J-36	12.1 kg	56	(684)	79	(952)	135	(1,636)	42	51
Mean		71 ± 12 ml/kg		60 ± 14 ml/kg		131 ± 9 ml/kg		55 ± 9	64 ± 6

animals from both control and CO-exposed animals were normal.[37] The reticulocytosis was never impressive, although those in the CO group were higher than the controls during the first eight weeks. By sampling every two weeks, we could have missed an early rise in reticulocytes.

Tables V and VI summarize the blood volume studies using Cr^{51}-labeled red cells. These measurements were made during the last two weeks of the exposure with the CO-exposed group compared to the controls. Table VII compares the mean values between both groups. The total blood volume was greater in both exposed species. The blood volumes of the exposed monkeys and dogs were, respectively, 39% and 31% greater than the volumes found in the control animals. This change was due primarily to an increase in the red cell mass, since the plasma volume was essentially the same in the controls and in CO-exposed dogs, and slightly less in the CO monkeys. The measured venous hematocrit averaged 66% in monkeys and 64% in dogs. The

TABLE VI

EFFECTS OF CHRONIC CARBON MONOXIDE ON BLOOD VOLUMES

Animal No.	Body Wt.	RBC Vol. ml/kg	RBC Vol. (ml)	Pl. Vol. ml/kg	Pl. Vol. (ml)	Bl. Vol. ml/kg	Bl. Vol. (ml)	Calc Hct.	Venous Hct
Control–Monkeys									
G-60	3.03 kg	23	(69)	52	(159)	75	(228)	30	38
H-14	3.10 kg	20	(61)	43	(143)	63	(195)	31	39
H-19	2.95 kg	23	(68)	47	(139)	70	(207)	33	41
G-34	5.03 kg	21	(108)	48	(244)	70	(352)	31	40
G-52	3.07 kg	23	(72)	59	(181)	82	(253)	28	37
Mean		22 ± 1 ml/kg		50 ± 6 ml/kg		72 ± 7 ml/kg		31 ± 2	39 ± 2
Carbon Monoxide Exposed–Monkeys									
G-54	3.5 kg	48	(170)	55	(193)	104	(363)	47	62
G-40	5.4 kg	60	(325)	39	(213)	100	(538)	60	70
G-32	5.0 kg	52	(262)	38	(190)	90	(452)	58	71
G-64	3.4 kg	54	(183)	54	(182)	107	(365)	50	60
Mean		54 ± 5 ml/kg		47 ± 9 ml/kg		100 ± 7 ml/kg		54 ± 6	66 ± 6

TABLE VII

EFFECTS OF CHRONIC CARBON MONOXIDE ON BLOOD VOLUMES (MEAN VALUES)

	Control (5)†	CO-Exposed (4)	Change of Mean Values
Monkeys			
Red cell volume*	22 ml ± 1	54 ml ± 5	+145%
Plasma volume*	50 ml ± 6	47 ml ± 9	−6%
Blood volume*	72 ml ± 7	100 ml ± 7	+39%
Calculated total hematocrit	31% ± 2	54% ± 6	+74%
Measured peripheral venous hematocrit	39% ± 2	66% ± 6	+69%
Dogs			
Red cell volume*	42 ml ± 6	71 ml ± 12	+69%
Plasma volume*	58 ml ± 4	69 ml ± 14	+3%
Blood volume*	100 ml ± 8	131 ml ± 9	+31%
Calculated total hematocrit	42% ± 3	55% ± 9	+30%
Measured peripheral venous hematocrit	48% ± 3	64% ± 6	+33%

* Milliliters per kilogram of body weight

† Number of animals in parentheses

differences between the calculated total hematocrit and the measured venous hematocrit are in keeping with the 9% difference known to exist between the two measurements, i.e., total body hematocrit = 0.91 venous hematocrit.[39]

Conclusion: In this entire study, the most impressive effect of continuous long-term CO exposure was the marked erythrocytosis. This most likely represents an adaptation to the chronic hypoxic stimulus induced by carbon monoxide. This long-term exposure did not produce the widespread changes in brain reported by others who worked at lower levels of CO. The cardiac changes were confined to rats only. In general, the adverse effects were surprisingly few. It is probable that under these chronic conditions, the additional hemoglobin produced was sufficient enough to provide the additional oxygen-carrying capacity necessary to avert oxygen deprivation in the tissue.

The Effects of Continuous Long-Term Exposure on the Performance of Rhesus Monkeys

Carbon monoxide is not considered life threatening in healthy individuals until blood COHb levels exceed 30%.[40] However, if the CNS is impaired at much lower levels of COHb so that performance is compromised, then it can be life threatening in situations requiring optimum performance. Back initiated a series of experiments in 1967 to determine if continuous long-term low level CO exposure might affect performance. The aim was to establish the level of CO that could be tolerated for prolonged periods of time without performance decrement.[39-41]

The performance program utilizing adult rhesus monkeys (*Macaca mulatta*) is outlined in Table VIII. The development of the program and the training of the monkeys were done at Holloman Air Force Base and have been described in detail previously.[41-43] The program evaluates operant avoidance behavior in monkeys utilizing continuous and discrete avoidance tasks. The specific program is as follows. (1) Dual continuous avoidance (CA) — two red lights mounted on a panel, one each over a right and left response lever, signal the start of the session. Both levers must be pressed within 15 seconds and every 15 seconds thereafter for 15 minutes or a shock is given. (2) Superimposed on the CA schedule are two discrete avoidance tasks as follows. (a) Auditory response time (ART) —during each 15-minute session, 12 randomized auditory signals (2,800 cps, 80 db) are presented, and the specific auditory response button must be depressed within two seconds or a shock is given. The response time following the cue is recorded as the ART. (b) Visual response time (VRT)— again during each 15-minute period, 12 randomized visual signals (yellow light) are presented, and the specific visual response button must be depressed within two seconds or a shock is given. The response time following the visual cue is recorded as VRT. Thus, each 15-minute session includes three tasks, i.e., a right and left lever must each be pressed once every 15 seconds continuously, and 12 visual and 12 auditory cues are also randomly presented. The monkeys worked 15 minutes every hour for eight hours a day, five days per week.

TABLE VIII

OPERANT BEHAVIOR IN MONKEYS (AVOIDANCE)

Program
Dual continuous avoidance (CA)
Right and left lever presses every 15 seconds for 15-minute session
Superimposed on CA schedule
1. Auditory response time (ART)
12 randomized auditory signals (2,800 cps, 80 db) every 15-minute session. Response < 2 seconds
2. Visual response time (VRT)
12 randomized light signals (yellow light) every 15 minute session. Response < 2 seconds
Work schedule
15 minutes every hour for 8 hour day
5 day week – Monday to Friday

Each study consisted of two weeks of baseline data being collected prior to CO exposure under conditions similar to the exposure, except for the presence of CO. The animals were then exposed continuously to CO, and the performance data collected during the exposure were compared to the baseline data for each animal.

Table IX summarizes all of Back's studies over the past two years.[39-41] Except for the first exposure, all others were done at altitude (5 psi, 68% O_2, 32% N_2). Included in the table are the exposure concentrations of CO, the duration of exposure, the respective COHb levels, the mean rise in hemoglobin concentration, and the over-all performance. In particular, the table shows that for the entire series only two animals showed altered performance at CO concentrations of 220 and 440 mg/cu m in Study I. The mean COHb levels were 19.5 and 30.1%, respectively, at those two levels of exposure. During Study I following exposure for 105 days to 55 mg/cu m of CO at altitude, the CO concentrations were doubled over three successive weeks, causing the mean COHb levels to rise from 4.7 to 30.1%. During this step-up phase, 6 of 12 animals appeared outwardly to be "ill," which was associated with a marked reduction in food consumption at the 440 mg/cu m level. Despite this, only two monkeys showed performance changes. However, in Study II, using 12 newly trained unexposed monkeys, no decrements were noted during exposure to 220 and 440 mg/cu m of CO for 100 days and 99 days, respectively.

Fig. 4 represents the mean performance levels for all monkeys during segments of a 100-day exposure to 220 mg/cu m of CO at altitude. These data are typical of the kinds of results we have obtained at all exposure levels of CO. In the particular study shown by Fig. 4, the performance levels span a period which includes two weeks of baseline data, the last 10 days of the exposure, the immediate postexposure period, and three weeks

TABLE IX

EFFECTS OF CHRONIC CO EXPOSURE ON RHESUS MONKEY PERFORMANCE

CO Conc. (mg/cu m)	Atmosphere	Duration (Days)*	Blood COHb (% Sat.) Mean	Range	Mean Rise Hb Conc. Above Control	Performance Total Animals	Animals with Decrement
Study I							
55	Ambient	100	3.7	(2.0-5.0)	+0.6 gm %	12	0
55	5 psi † mixed gas‡	105	4.7	(4.0-6.0)	+1.4 gm %	12	0
110	5 psi, mixed gas	7	8.3	(7.0-10.0)		12	0
220	5 psi, mixed gas	7	19.5	(17-21)		12	2
440	5 psi, mixed gas	7	30.1	(27-34)		12	2
Study II							
220	5 psi, mixed gas	100	21.6	(20-24)	+3.3 gm %	12	0
440	5 psi, mixed gas	99	31.2	(28.5-34)	+3.5 gm %	12	0

* Days = days of continuous exposure

† 5 psi equivalent to 27,000 feet altitude

‡ Mixed gas = 68% O_2, 32% N_2

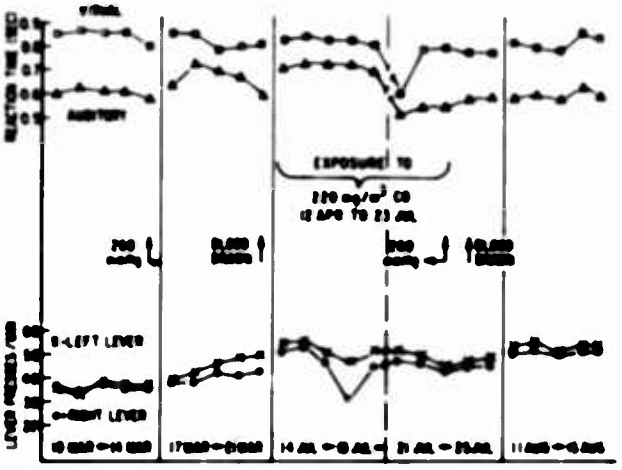

Fig. 4. Mean performance levels for 12 rhesus monkeys exposed to 220 mg/cu m of CO for 100 days.

postexposure. It can be seen that, in general, there were no significant differences in performance levels over the entire period of study. The visual response times (VRT) remained close to 0.8 seconds, and the auditory response times (ART) varied between 0.5 and 0.7 seconds. The average number of lever presses was essentially the same throughout.

Figs. 5 and 6 represent the performance levels of the only two monkeys in the entire series of exposures which showed any performance changes of significance. As previously mentioned, both showed the altered performance in Study I at the 220 and 440 mg/cu m CO levels. Prior to that time, the animals performed

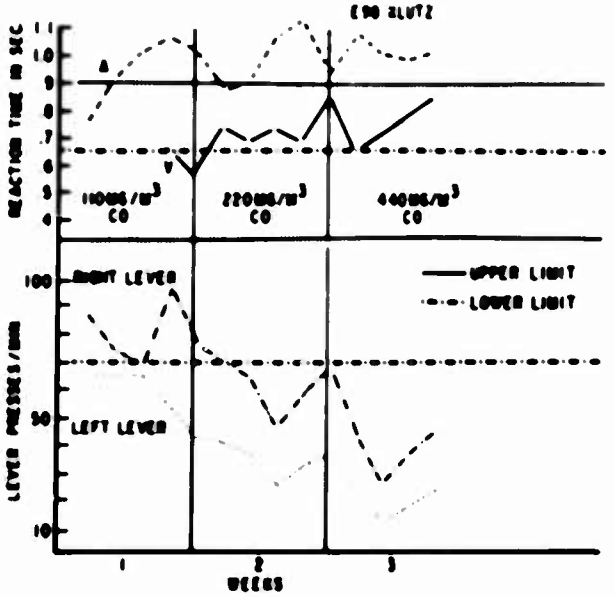

Fig. 5. Altered performance in rhesus monkey (see text).

normally. Fig. 5 shows the performance of monkey E98 over the last three-week period of involvement. This monkey shows the slowing of lever presses below his established normal limits and an increase in auditory response times during the transition from 110 to 440 mg/cu m of CO. Fig. 6 shows the performance level of M82, the other involved monkey. Prior to increasing exposure levels from 55 to 110 mg/cu m of CO, this animal increased left lever presses, without changes in the other parameters. At the 110 mg/cu m level he

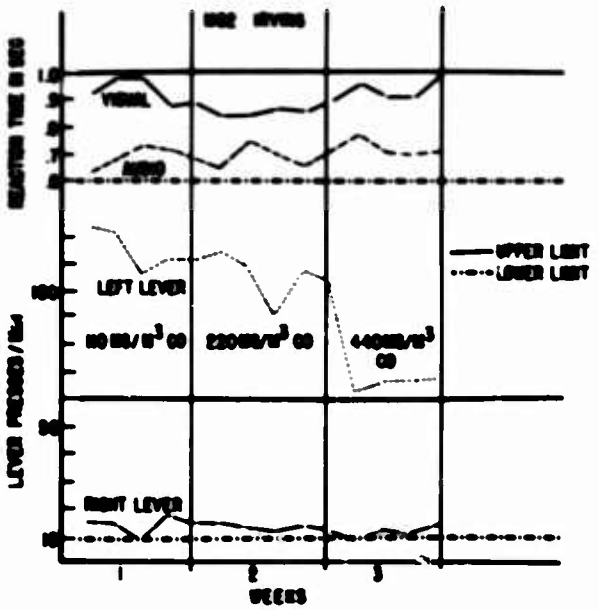

Fig. 6. Altered performance in rhesus monkey (see text).

maintained this pattern, but at 220 and 440 mg/cu m left lever presses began to fall off sharply, whereas right lever presses remained constant or fell slightly. To call this a performance decrement may not be appropriate, but certainly it can be considered altered since the left lever presses never decreased below the original baseline.

Conclusion: In general, carbon monoxide up to 440 mg/cu m did not appear to impair operant behavior in monkeys. A criticism of this performance program is that it is not sensitive enough to indicate subtle changes, and the animals must be virtually overwhelmed before they cease to perform well. For this reason, we are establishing new programs for use in psychopharmacology which are not as robust. However, it is also apparent that at COHb levels of 30% the animals certainly were capable of performing learned tasks.

The Effects of Short-Term Low Level Carbon Monoxide Exposure on Human Performance

It is frequently difficult to extrapolate data from animal studies to the human, and, ultimately, man must be tested. This is especially true in the case of carbon monoxide, since recent reports indicate that COHb levels as low as 2 to 5% have caused performance decrements in humans. There have been conflicting reports over the years regarding this, and they are too numerous to cite for our purposes here. However, the two recent studies that have made an appreciable impact include those of Schulte[31] and Beard and Wertheim.[32] Schulte reported impairment of cognitive and psychomotor performance at 5% COHb levels with some tendencies for disruption as low as 2% COHb. Beard and Wertheim showed impaired auditory discriminability of tone lengths with COHb levels of approximately 4 to 5%. The implication of these studies is that CO may be more of a risk than once thought. If valid, such a risk is extremely important in the aerospace environment where extremely sophisticated performance is required of the human.

At Wright-Patterson Air Force Base, O'Donnell, Mikulka, Heinig and Theodore studied the effects of low levels of CO exposure on human performance.[33-38] In the main study, 10 male university students between the ages of 19 and 22, in good health and supposedly nonsmokers, were exposed for three hours to 0, 50 and 125 ppm CO in closed chambers (Thomas Domes).[36] The subjects spent a three-hour session at each of these levels, and the order of exposures was counterbalanced to avoid sequence effects. A double-blind procedure designed to include not only the subjects and experimenters, but also all technicians that worked in the general area, was employed through the study.

Following the main study, five subjects were exposed to 200 ppm CO, and three to 250 ppm. The program was essentially the same except that the experiment was not double-blind, counterbalancing was not possible, and the subjects were told they would be receiving higher levels of CO. Because of the small number of subjects, no statistical analysis was performed on the additional data.

Performance was assessed using three tasks: (1) a highly cognitive task — time estimation; (2) a psychomotor tracking task; and (3) the Pensacola Ataxia Battery. The tasks are described in brief as: (1) time estimation: During each testing interval, the subjects were required to make a series of estimates of a 10-second "empty" interval. At a signal from an experimenter, the subject began estimating 10-second intervals and continued until told to stop (after three minutes). All estimates were automatically recorded. The subjects were never told of the accuracy of their estimates. (2) Critical instability tracking task (CITT): This tracking task was developed by Jex and is described in great detail elsewhere.[39,40] This is a very difficult psychomotor task in which the electronic characteristics of the system require the subject to stabilize a statically unstable controlled element by closing a compensatory loop around the system in order to keep a needle on a display dial from going off scale. This is done by manipulation of a control stick. The subject's optimal strategy is to maintain control stick displacement in an exact proportion to the system output (needle deflection). The task is made more difficult linearly over time which forces the subject to make greater and quicker compensations. A point is reached where the subject cannot possibly respond quickly and accurately enough to maintain control. The point of control loss is converted into a difficulty level score, and the reciprocal of this difficulty level is considered a measure of the subject's complex reaction time. In order to describe the functions involved, this task is most closely related to performances requiring marked perceptual-motor coordination with strong requirements for speed and accuracy. (3) Pensacola

TABLE X

CARBOXYHEMOGLOBIN LEVELS FOR ALL SUBJECTS FOLLOWING THREE HOUR CO EXPOSURES

Subject No.	0 ppm	50 ppm	125 ppm	200 ppm	250 ppm
1	0.7	2.8	6.5		
2	1.2	2.4	6.6		
3	0.8	2.7	6.5	9.8	
4	1.0	3.1	7.4		13.1
5	1.0	3.0	6.8		
6	1.3	3.6	6.8	10.1	11.9
7	1.1	3.3	6.4	10.0	
8	0.9	3.0	6.6	10.9	
9	0.6	2.9	6.2	10.9	12.1
10	3.5	4.5	7.4		
Mean*	0.96	2.98	6.64	10.35	12.37

* Does not include scores for Subject No. 10

Ataxia Battery: Tasks were used from this battery which consist of a number of balancing tasks performed either on narrow rails or on the floor.[39]

A session consisted of a three-hour exposure starting from the time the subject entered the Thomas Dome. The CO levels were established prior to entry. The subjects performed 15 minutes out of every 30 during which they had five trials on the CITT, three minutes of time estimation, and then five more tracking trials. Following 90 minutes of exposure, they were permitted to walk and stretch within the dome to reduce fatigue and boredom effects. The subjects were always in constant communication with the experimenters via headphones. It was considered extremely important that the subjects be able to see outside the domes to preclude sensory restriction effects which could mimic or confound CO effects. Following the three-hour exposure, venous blood was drawn for COHb, Hb and hematocrit. The Pensacola Ataxia Battery was performed immediately thereafter.

Table X summarizes the blood COHb levels from the 10 subjects measured at the end of each session. The mean data do not include that from subject No. 10. On the basis of a COHb of 3.5% at an exposure of 0 ppm CO, he was questioned and admitted to being a smoker. All his performance data were excluded from analysis. The mean COHb data shown are in excellent agreement with that predicted from the CO uptake curve constructed by Forbes et al.[39]

Fig. 7 shows the group mean data for nine subjects at 0, 50 and 125 ppm CO on the critical instability tracking task. For each subject, the mean difficulty level was obtained from each set of 10 trials for every test period. Each subject had six sets of scores for each level of exposure. In evaluating the performance data, one must realize that the CO burden continues to increase with time over this short course of exposure. Although the atmospheric concentration of CO is constant, the accumulation within the body is a function of time. Thus, it is important not only to compare the differences between the conditions, but also to evaluate the trends occurring within each condition over the three hours of exposure. It can be seen (Fig. 7) that no trend toward poorer performance appeared in any of the three conditions. In fact, there is a tendency to improve over time for all conditions. Statistical analysis done independently for each exposure level to determine whether performance changes had occurred over the course of the exposure failed to reveal any clear changes. The only condition that showed any change at all indicated that performance became better during exposure to 125 ppm CO. Statistics comparing the mean data among the three exposure levels revealed a difference in performance levels at the 105- to 120-minute period which completely disappeared by the last period. At the 105- to 120-minute period, Newman-Keuls analysis showed that performance under 0 ppm CO was better than either of the two CO conditions ($P < .05$), while at the 135- to 150-minute interval, performance at 0 ppm CO was not different than at 125 ppm and only marginally better than at 50 ppm. There were no significant differences in the CO groups at these two periods. If performance trends are examined, this transient effect is seen to be not due to performance decrements in the CO group, but due to a transitory increase in performance under the 0 ppm condition. Evaluation of individual performance curves revealed no consistent differences as a function of CO exposure.

Fig. 8 shows the additional tracking studies done at 200 ppm and 250 ppm CO. Due to the limited number of subjects, these were not statistically analyzed. However, they appear similar in both conditions with no trend toward poorer performance over time.

It can be assumed that as CO uptake increases over time, performance would be expected to show a decrement if there were any simple relationship between the two. There was no over-all time-related decrement seen in any of the CO runs up to 250 ppm in

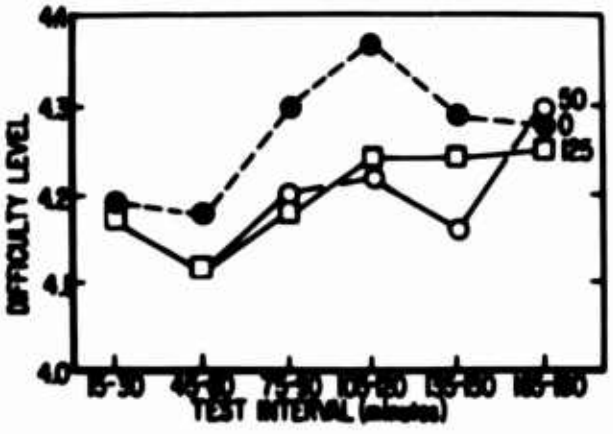

Fig. 7. Human tracking performance at 0, 50 and 125 ppm CO compared over time.

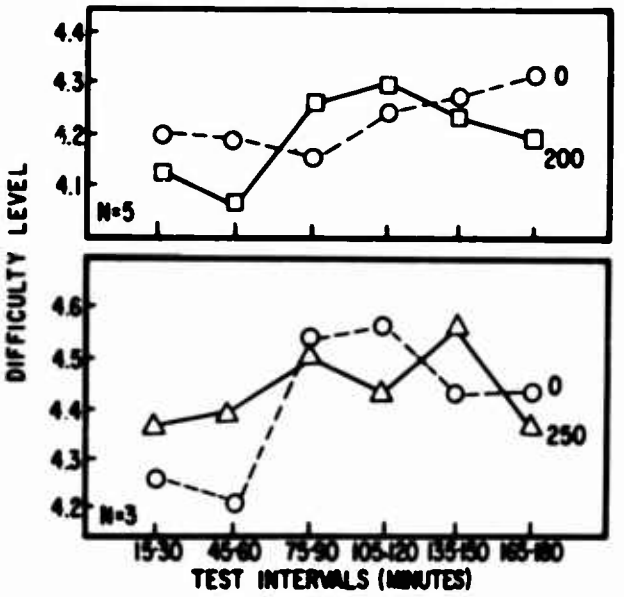

Fig. 8. Human tracking performance at 200 and 250 ppm CO compared over time.

any of the subjects. Thus, CO appeared to have no effect on tracking performance up to 125 ppm and probably none as high as 250 ppm.

The performance curves for time estimation are presented in Fig. 9. Each point represents the group mean estimates at the respective exposure interval. A curve for each of the three exposure levels is shown. It is apparent that although there is some separation among the different conditions, there is no over-all trend to overestimate or underestimate as a function of CO uptake. Actually, there is a slight tendency, for all conditions, to increase accuracy over time. A very similar pattern is seen for subjects exposed to 200 and 250 ppm CO in Fig. 10. Of note, although only three subjects were exposed to 250 ppm CO, their estimate of 10 seconds was the most accurate of any. Statistics done on the 0, 50 and 125 ppm conditions revealed no significant decrement in performance within any exposure condition over time.

Statistically comparing the three conditions at each time interval, a transient difference was revealed at the 135- to 150-minute period which disappeared by the last period. The time estimates were longer under 50 ppm CO than under the control condition as determined by the Newman-Keuls test ($P < .05$). However, Fig. 9 reveals that this difference arose from changes in the 0 ppm condition, and not from poorer estimates under the CO conditions. The total difference is less than one second, and since no differences are found between the 0 and 125 ppm CO conditions, it is difficult to construe this as a CO effect.

Again, as in the case of tracking performance, CO up to 125 ppm, and most probably as high as 250 ppm, had no apparent effect on the ability to estimate 10-second "empty" time intervals.

Seven tests from the Pensacola Ataxia Battery were utilized in this study. CO exposure under the conditions

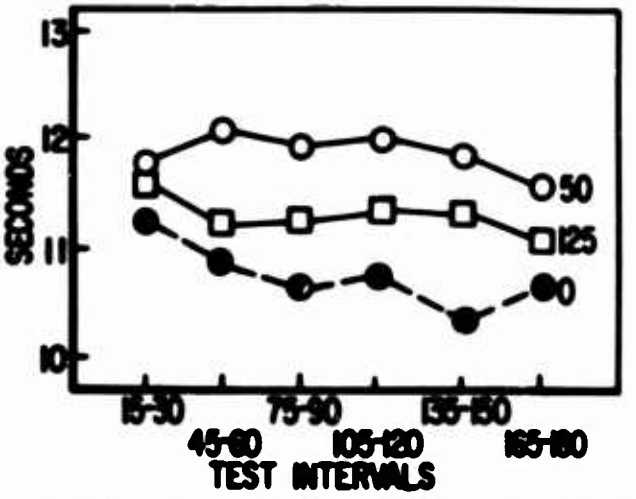

Fig. 9. Mean estimates of the "empty" 10-second interval at 0, 50 and 125 ppm CO compared over time.

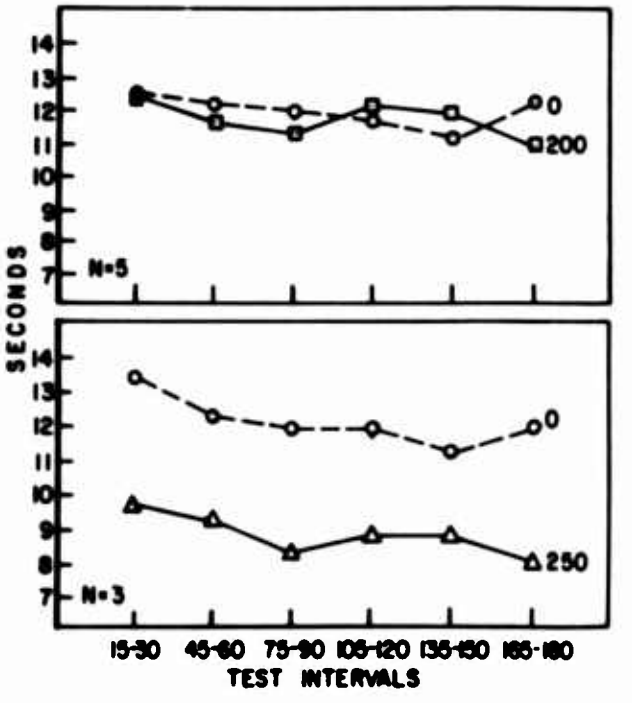

Fig. 10. Mean estimates of the "empty" 10-second interval at 200 and 250 ppm CO compared over time.

of these experiments had no effects on the kinds of abilities measured by these tests.

This study attempted to determine whether short-term low level CO exposure affected human performance by using a broad range of performance measures. On an ordered scale, these tasks ranged from the heavily cognitive task of estimating time, during which the subject supplied his own counting stimuli, and the tracking task which required the coordination of visual input with rapid motor responses, to the psychomotor task involving vestibular and gross motor controls for dynamic equilibrium. The results indicated that three hours of exposure to CO levels up to 125

ppm, and probably as high as 250 ppm, produced no performance decrement in any of these parameters.

The results of this study are in conflict with studies previously cited, the most notable being that of Beard and Wertheim. In their study using a temporal auditory discriminability task, they found major disruptions at levels as low as 50 ppm CO. It should be noted that their subjects were confined to a soundproof audiometer booth with a volume of 100 cu ft. There was no outside visibility and the tasks did not involve a great deal of kinesthetic, proprioceptive or visual input to the subjects. In view of the fact that even moderate degrees of sensory or motor restriction can cause significant perceptual and motor distortions,[60] it is possible that their reported CO effects could be accounted for, or at least contributed to, by sensory restriction effects. In contrast, this study especially aimed to avoid such factors.

Conclusion: The main issue at hand is to determine a set of realistic conditions which can be applied in predicting what will impair pilot performance in an aircraft environment. Our study was specifically designed with this aspect in mind. Carbon monoxide within the conditions of these experiments does not appear to impair the kinds of abilities required to perform space docking procedures, instrument landings of aircraft, or high speed automobile driving.

Summary and Conclusions: The possibility that chronic exposure to low concentrations of carbon monoxide may have adverse effects on humans has become a major issue. Unfortunately, the literature offers no clear-cut solutions to this problem, since a number of published studies contain conflicting results. To speculate on the differences seen in the various studies would be indeed an awesome task. Those in which human performance was assessed in particular showed the greatest variability. In such cases, the lack of uniformity among the investigators in controlling multiple stressors, or differences in exposure techniques, might explain some of the variability. Regardless of differences, the real difficulty that arises is how to apply these data in determining realistic levels for carbon monoxide which are safe. Such data obtained under realistic conditions for defining those levels of carbon monoxide are important to the Air Force. It is necessary for the design of life support systems for closed environments, where the human operator may perform complex functions for extended periods of time. This information in addition has application to today's modern industrial complexes which are located in those urban areas where environmental CO levels tend to be highest.

The work reviewed in this paper is an effort toward defining safe levels for carbon monoxide. In general, carbon monoxide was evaluated from three different approaches, and a relative paucity of detrimental effects were found under low level exposure conditions, both acute and chronic. Exposure to relatively high levels of CO (460 and 575 mg/cu m) for 168 days had no apparent effect on animal survivability, growth rates or clinical chemistry and failed to produce pathologic changes in the CNS. Although rats showed some cardiac hypertrophy, all the larger animals, including dogs, baboons, and monkeys, failed to show cardiovascular changes. The most prominent effect due to CO was the marked erythrocytosis seen during chronic exposure. This undoubtedly represented an adaptation to chronic tissue hypoxia induced by CO. Chronic exposures to a series of CO levels up to 440 mg/cu m failed to produce decrements in the operant behavior of rhesus monkeys.

Although caution is warranted in extrapolating animal studies to the human, the findings in these studies certainly show that mammalian species are able to tolerate carbon monoxide quite well under the conditions employed. Finally, no performance decrements were found in humans during three-hour exposures of 50 to 250 ppm CO. It is concluded that if CO at these levels had an initial adverse effect, adaptive processes must take place early during exposure, and the compensatory changes override the initial CO effect.

We do not wish to leave the reader with the impression that we are opposed to more stringent control of environmental pollution or that carbon monoxide is completely harmless. The general public, and those responsible for its general health, must establish levels for carbon monoxide which contain wide safety margins to insure the well-being of the total population. However, these limits must be established by realistic criteria in order to be meaningful. In the case of the Air Force, which deals with a more select population, it needs such criteria in order to operate within the economic and practical engineering constraints placed on operational systems and still be certain that the human element is unimpaired.

(Dr. Back)
6570th Aerospace Medical Research Laboratory
Wright-Patterson Air Force Base
Ohio 45433

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